Significant role of macrophages in human cancers associated with Epstein-Barr virus (Review)

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Abstract. Epstein-Barr virus (EBV) is a ubiquitous pathogen that was first identified as a human cancer virus. Many human cancers are associated with EBV, and we demonstrated that EBV infects macrophages. Macrophages infected with EBV show a close correlation with many human cancers, and thus more attention must be given to the role of macrophages infiltrating into cancer tissues associated with EBV. In this review, I discuss the role of macrophages in the process of EBV-associated oncogenesis with regard to interleukin-10.

Contents

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Abbreviations: ALCL, anaplastic large-cell lymphoma; BCRF1, *Bam*HIC coding rightward reading frame-1; BZLF1, *Bam*HIZ coding leftward reading frame-1; CIN, cervical intraepithelial neoplasia; CTCL, cutaneous T-cell lymphoma; EBER1, EBV-encoded non-polyadenylated RNA-1; EBNA LP, EBV nuclear antigen leader protein; EBNA2, EBV nuclear antigen-2; EBV, Epstein-Barr virus; IL-10, interleukin-10; ISH, *in situ* hybridization; LCH, Langerhans cell histiocytosis; LMP1, latent membrane protein-1; NPC, nasopharyngeal carcinoma; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; TAM, tumor-associated macrophage

Key words: Epstein-Barr virus, human cancer, macrophages, tumor-associated macrophages, *in situ* hybridization

1. Introduction

Of the 12.7 million new cancer cases that occurred in 2008 in the world, the population-attributable fraction for infectious agents was 16.1%, and that of Epstein-Barr virus (EBV) was 5.4% (1). EBV is a ubiquitous virus that infects almost all adults throughout the world. EBV is also known as a causative agent of i) Burkitt's lymphoma, an endemic malignant tumor in East African children; ii) nasopharyngeal carcinoma (NPC), which has a tendency of high occurrence in the Chinese and iii) various tumors associated with immuno-suppressive states such as those observed post-transplantation and in AIDS (2,3). Although foods, environment, and genetic differences must be considered, I hypothesized that more human tumors are generated by EBV infection than has been reported, and to test this hypothesis EBV transcripts were examined in various human tumors with mRNA *in situ* hybridization (mRNA ISH) and immunofluorescence staining. The results of these procedures showed that EBV infects and proliferates in macrophages. The neoplasms of macrophage-related cells were also investigated. Seven types of cancer other than NPC, four types of lymphoma, and Langerhans cell histiocytosis (LCH) expressed EBV transcripts, including its oncogenes. None of the patients examined herein showed an immunocompromised state, and most of the patients with LCH were North American. Here, I review the recent reports correlating EBV transcripts with human cancers, and I discuss the role of macrophages in the oncogenesis of EBV.

2. *Bam*HIW

*Bam*HIW is a leader sequence of some EBV transcripts. EBV contains multiple copies of a 3-kb *Bam*HIW repeat sequence. A better detection effect can thus be expected with the use of this sequence as the probe for mRNA ISH. I treated to remove 830 bases containing the 'Alu-family'-like sequence from the *Bam*HIW fragment, and used the resulting 2.27-kb sequence for the mRNA ISH (4). *Bam*HIW transcripts were detected in almost all of the neoplasms examined (Table I).

Although breast cancers were not examined, a 1995 study that used polymerase chain reaction (PCR) over a region of

*Bam*HIW found that 21% of the breast cancer specimens evaluated were positive for EBV DNA (5). Tierney *et al* reported that the five-repeat number of *Bam*HIW was most effective for B-cell transformation (6).

3. EBV leader protein

Allan *et al* reported that EBV leader protein (EBNA-LP) transfectants grew faster than control cells (7). Peng *et al* showed that EBNA LP is a gene-specific coactivator of EBNA2 (8). We showed EBNA-LP expression in various human cancers (9). Portal *et al* reported that EBNA-LP dismisses the transcription repressors NCoR and RBPJ from promoters and enhancers, and that EBNA-LP and transcription factors act in the repressor deletion and gene activation necessary for lymphoblastoid cell line growth and survival (10).

4. EBV nuclear antigen-2

Tumorigenicity of EBV nuclear antigen-2. In a previous study, I demonstrated that EBV nuclear antigen-2 (EBNA2) is a strong oncogene of EBV (11). After a 2-3-week inoculation of a transfected rat fibroblast cell line with a recombinant EBNA2 expression plasmid, four of seven clones reproducibly formed tumors in nude mice. All of these tumorigenic clones could be grown in low serum, and two of the four tumorigenic clones formed colonies in soft agar. These four tumorigenic clones showed EBNA2 expression, but the non-tumorigenic clones did not. These results indicate that the expression of EBNA2 is correlated with tumorigenicity.

Detection of EBNA2 expression. The mRNA expression of EBNA2 can be detected with the mRNA ISH protocol that we established (12), and the EBNA2 protein expression can be detected with indirect immunofluorescence staining using a monoclonal antibody.

Other functions of EBNA2. In 2009, Pan *et al* indicated that EBNA2 disrupts the mitotic checkpoint and causes chromosomal instability; this was a newly discovered function of EBNA2 in cell-cycle regulation (13). More recently, Sano *et al* reported that EBNA2-deleted EBV can infect rabbits with lower efficiency than prototype EBV (14). This finding suggests that oncogenicity and infectivity may be correlated, although these two functions have been described as independent in the case of EBV-encoded nonpolyadenylated RNAs (EBERs) (15).

Rosato *et al* found that EBNA2 regulates microRNA (miR)-21 and miR-146a (16). EBV contains microRNAs near the downstream of EBNA2 and exploits RNA silencing as a convenient method for gene regulation in a nonimmunogenic manner (17).

5. Latent membrane protein-1

The transformation of mouse cells by the latent membrane protein-1 (LMP1) gene of EBV was reported by Baichwal *et al* (18). LMP1 was reported to have a role in the carcinogenesis of NPC (19). Kim *et al* also showed that the transformation of canine kidney epithelial cells by LMP1 formed spheroidal cysts in collagen gel matrix and induced invasive growth (20). Shair *et al* compared the development of papilloma and carcinoma in epithelial cells of transgenic mice with model carcinogens DMBA and TPA, and they found that LMP1 was a weak promoter, that it increased papilloma formation, and that it slightly increased squamous cell carcinoma (SCC); the development of SCC was significantly increased in LMP2A double-transgenic animals (21).

6. EBV-encoded non-polyadenylated RNA-1

Although Swaminathan *et al* reported in 1991 that EBER-deleted recombinant EBV transformed lymphocytes (22), many reports describing EBER oncogenesis have accumulated since that date (23,24). Most EBV-encoded non-polyadenylated RNA-1 (EBER1) detection has been accomplished with commercial RNA ISH kits, whereas I examined EBER RNA ISH with probes I prepared myself. Although many copies of EBER1 exist, there is a report that false-negative results are most often observed (25). Almost all of the English language studies regarding EBV-associated neoplasms and EBV expression used EBER1 RNA ISH alone. However, this method needs to be further investigated. Through my experiences with mRNA ISH results, I observed that relatively higher sensitivity was achieved with *Bam*HIW mRNA ISH compared to EBER1 RNA ISH (Table I).

7. EBV transcripts and human diseases

I examined many human tumors: mesopharyngeal and hypopharyngeal carcinoma (26) as well as NPC (27), oral cancer (9,28), thyroid carcinoma (9,29), renal cell carcinoma (RCC) (30), testicular tumors (4,9), uterine cervical carcinoma (12,31), anaplastic large-cell lymphoma (32,33), cutaneous T-cell lymphoma (9,34), leptomeningeal lymphoma (35), lymphoproliferative diseases in the lung (36) and LCH (37) by means of *Bam*HIW, EBNA LP, EBNA2 mRNA ISH and EBER1 RNA ISH, and by immunofluorescence staining using monoclonal EBNA LP, EBNA2, LMP1, and BZLF1 (*Bam*HIZ coding leftward reading frame-1) antibody. The recent reports concerning these diseases, in which I examined EBV transcripts, are discussed below.

Mesopharyngeal and hypopharyngeal carcinoma. No new reports are available.

Oral cancer. Using an LMP1-specific antibody, Shamaa *et al* found that EBV and DNA topoisomerase II correlate with oral epithelial dysplasia and oral SCC (38). Slots *et al* reported that they detected EBV DNA in 60-80% of aggressive periodontitis lesions and in 15-20% of gingivitis lesions or normal periodontal sites (39). Jalouli *et al* reported that of 155 oral SCC samples examined, 85 were positive for EBV by nested PCR (40). Szkaradkiewicz *et al* found that 12 of 14 cases of tonsillar carcinoma and 12 of 14 cases of tongue carcinomas showed EBV DNA positivity with PCR, and they reported that EBV was associated with these carcinomas much more frequently compared to human papilloma virus (41). DNA was detected in 19.2% of oral SCCs and the expression of LMP-1 was found in 85.7% of EBV-positive oral SCCs (42). In

another examination, EBV DNA was detected in 15.2% of oral SCCs (43). Frangou *et al* reported the rare detection of EBV replication in tongue epithelial cells (44,45). Walling *et al* described that approximately 1 in 10^5 pre-Langerhans cells harbor latent EBV infection *in vivo*, a frequency similar to B lymphocytes in healthy individuals, and they proposed a new model of EBV transition from blood to oral epithelium; they speculated that the infected Langerhans cells serve as a reservoir of EBV in oral epithelial cells (46).

Thyroid carcinoma. A rare case of thyroid involvement by malignant histiocytosis of the Langerhans cell type was reported in 1996 (47), but its association with EBV is unclear. There are many reports regarding LCH co-existing with papillary thyroid cancer, but none of the relevant studies examined EBV. Furthermore, some reports described that numerous tumor-associated macrophages (TAMs) were distributed in advanced thyroid cancer and thyroid papillary carcinoma, and that an increased density of macrophages is associated with decreased survival, but none of these reports mentioned an association with EBV (48,49).

Renal cell carcinoma. EBV infection was reported in sarcomatoid renal cell carcinoma (RCC) tissues (50). In my experience, one case of sarcomatoid RCC expressed EBV transcripts (30). There is a report that gastric cancer and concomitant RCC were both positive for EBV (51).

Testicular carcinoma. Although there are some negative reports concerning testicular cancer and EBV (52,53), EBV in relation to testicular cancer risk (54) and EBV infection and the risk of testicular cancer in offspring (55) have been described.

Uterine cervical carcinoma. There are many reports of EBV association with uterine cervical carcinoma, but almost all used data obtained by PCR; the detection of EBV transcripts is very rare. Using nested PCR, Santos *et al* examined 66 women with high-grade cervical intraepithelial neoplasia (CIN) and 14 women with invasive cervical cancer, and they found that the invasive cancer group showed significantly higher positivity for EBV (56). Kim *et al* showed similar results of EBV positivity, and they noted that p16 methylation was observed in the cases of EBV-positivity (57). Szostek *et al* found EBV integration in 50% of cervical SCCs, but not in CIN (58).

Anaplastic large-cell lymphoma. Since the WHO classification system was changed in 2004, cases of anaplastic large-cell lymphoma (ALCL) may not be the same as those before 2004. Here, I describe the ALCL according to the criteria of the classification at each period of time.

Kuse *et al* reported that EBV was detected with EBER1 ISH in 6 of 17 cases of $CD30^+$ ALCL, and all EBER1-positive cases showed LMP1 expression and 2 of those 6 cases showed EBNA2 expression with immunohistochemistry (59). Tazzari *et al* described an EBV-infected cell line which grows in SCID mice with the morphologic features of $CD30^+$ ALCL (60). EBV association in ALCL was also reported by Agarwal *et al* (61). A report from Pakistan showed that EBV DNA was amplified in 28 of 37 cases of ALCL (62). Another report from Korea noted that two of 16 $CD30^+$ ALCL cases showed EBER positivity by ISH (63). A study conducted in India showed that EBV DNA was amplified by EBNA1 and EBNA3C PCR in 4 of 6 ALCL cases (64). Ma *et al* presented a case report and discussion of 63 reported cases of EBV^+ ALCL (65). Although the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue 2008 edition states that ALCL is consistently negative for EBV, and many negative results were reported (66-69), reports of EBV-positive ALCL cases have been reported after 2008 (64,65).

Cutaneous T-cell lymphoma. Park and Ko reported that 5 of 12 cutaneous T-cell lymphoma (CTCL) cases showed EBER positivity by ISH (70), and Erkek *et al* showed that 9 of 92 subjects with mycosis fungoides (MF) evidenced EBV DNA (71). In a study by Novelli *et al*, 7 of 71 MF cases were EBV DNA-positive by PCR, but EBER signals were negative by ISH (72). Copur *et al* reported the full clinical recovery of a patient with EBV-associated CTCL after topical acyclovir treatment (73).

Langerhans cell histiocytosis. Although EBV DNA was detected in 3 of 19 LCH patients by PCR, no signal of EBERs in LCH cells was revealed by ISH, and thus the experiments did not support the role of EBV in the pathogenesis of 83 patients with LCH (74). However, there are some reports supporting EBV pathogenesis of LCH. Csire *et al* found that antiviral therapy effectively cleared EBV (75), which I also reported in 2004 with one patient (37). The development of LCH was also described with chronic active EBV infection (76). As shown in Table I, immunofluorescence of BZLF1 was detected in all LCH cases, which showed lytic infection occurring in LCH, and thus LCH was sensitive to acyclovir (37,75).

8. Lytic infection of EBV in neoplastic tissues

I frequently observed the lytic infection of EBV in human neoplastic tissues, and my review of the literature revealed the following. An EBV-positive epithelial cell tumor, gastric carcinoma, and NPC showed ganciclovir susceptibility, which indicated lytic infection of the tumors (77). Sporadic lytic viral replication was observed in breast carcinoma cell lines (78). In NPC cells, EBV lytic infection was reported to induce interleukin-10 (IL-10) in monocytes (79). The data regarding IL-10, monocytes and macrophages will be examined further in the 'Discussion' section. Viral reactivation from latency was controlled by the expression of BZLF1 of EBV, and Murata and Tsurumi recently found that histone H3 lysin 27 trimethylation and H4K20me3 markers are crucial for the suppression of BZLF1 (80). These results are expected to be useful in the development of therapy for EBV-positive cancers using epigenetic disruptors.

9. Radiation therapy for EBV-positive neoplasms

Our group reported increased sensitivity of EBNA2-transformed cells to ionizing radiation (81), and more recent studies have followed up on this finding. Plasma EBV DNA levels significantly decreased after radiotherapy (82). Among 270 patients with CTCL, complete response was observed in 255 patients treated with 700-800 cGy (83).

Table I. Summary of the results of several *in situ* hybridization and immunofluorescence protocols.

Disease (d) or cell line (c)	No. of samples	*In situ* hybridization				Immunofluorescence				PCR	Refs.
		*Bam*HIW	EBNA-LP	EBNA2	EBER1	EBNA-LP	EBNA2	LMP1	BZLF1		
d NPC	5	4/4			1/1		4/5	4/5	5/5		(27)
d MPC	37	35/35					5/8	3/8		6/6	(26)
d HPC	17	5/13								4/4	(26)
c MPC	5	5/5					3/5	4/5			(26)
c HPC	2	2/2					2/2	2/2			(26)
d Oral cancer	37	36/36	5/6	9/12	16/24	4/4	16/28	15/29	14/28	26/26	(28)
d Thyroid papillary cancer	10	10/10	0/2	2/10	6/8	1/2	2/10	2/10	2/10	9/9	(29)
d Thyroid undifferentiated ca	11	11/11	3/3	11/11	3/4	3/3	4/4	3/4	3/4	3/3	(29)
d Thyroid SCC	1	1/1		0/1	1/1		0/1	0/1	0/1	1/1	(29)
c Thyroid unfifferentiated ca	5	5/5		5/5	5/5	2/2	2/5	2/5	2/5		(29)
c Thyroid SCC	1	1/1		1/1	1/1	2/2	0/1	0/1	1/1		(29)
d Renal cell carcinoma	9	9/9	7/9	7/9	8/9	5/9	6/9	7/9	2/9	8/8	(30)
d Wilms' tumor	2	1/2	2/2	2/2	1/2	2/2	2/2	1/2	2/2		(30)
c Renal cell carcinoma	2	2/2	2/2	2/2	2/2	2/2	2/2	2/2	0/2		(30)
d Testicular tumor seminoma	16	16/16	5/5			5/5	3/6	5/6		9/9	(4)
d Testicular embryonal ca.	11	11/11	3/3			3/3	2/3	3/3		5/5	(4)
d Uterine cervical ca. CIN	22	16/21		4/5	6/17		6/13	4/8			(9,12,31)
d Uterine cervical ca. ICC	30	22/24		15/16	7/14		19/25	6/9			(9,12,31)
d Uterine cervical ca. SCC	9		8/9			1/3	3/3				(9,12,31)
d Uterine cervical ADSCC	2		2/2			2/2	2/2				(9,12,31)
d Uterine cervical adenoca.	2		2/2			1/1	1/1				(9,12,31)
d ALCL	7	7/7					3/6	2/2		6/6	(32,33)
d CTCL	12	12/12	4/4	7/10	5/6	1/2	11/12	5/12	9/12	8/8	(34)
d Lung LPD non-Hodgkin lym	2	2/2	2/2	2/2	2/2	1/2	2/2	2/2	2/2	2/2	(36)
d Lung LPD MALToma	5	5/5	5/5	5/5	5/5	4/5	5/5	3/5	5/5	2/2	(36)
d Leptomeningeal lymphoma	1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	(35)
Cultured macrophages	5	5/5					5/5	5/5		5/5	(84)
d LCH Japanese MFMS	4	4/4		4/4	2/4		4/4	3/4	4/4	1/1	(37)
d LCH Japanese MFUS	3	3/3		1/3	3/3		3/3	2/3	3/3	1/1	(37)
d LCH Japanese UF	10	10/10		8/10	9/10		9/10	10/10	10/10	7/7	(37)
d LCH North American MFMS	10	9/10	1/1	5/9	7/8	1/1	1/1	1/1	1/1		(37)
d LCH North American MFUS	12	5/9		4/7	8/10						(37)
d LCH North American UF	8	7/7		5/6	5/5						(37)

Table I. Continued.

Disease (d) or cell line (c)	No. of samples	*In situ* hybridization				Immunofluorescence				PCR	Refs.
		*Bam*HIW	EBNA-LP	EBNA2	EBER1	EBNA-LP	EBNA2	LMP1	BZLF1		
Total of diseases	296	243/264	51/57	93/124	96/134	35/46	114/162	81/132	58/93	98/98	
Total of cell lines	20	20/20		8/8	8/8	6/6	14/20	15/20	3/8		
Negative samples											
d Lung adenocarcinoma	10	1/10		0/3	0/2	0/1	0/1				Unpublished
d Lung SCC	4	0/4									Unpublished

c, cell line; ca, carcinoma; d, disease; ADSCC, adenosquamous cell carcinoma; ALCL, anaplasatic large-cell lymphoma; CIN, cervical intraepithelial neoplasia; CTCL, cutaneous T-cell lymphoma; HPC, hypopharyngeal carcinoma; LCH, Langerhans cell histiocytosis; ICC, invasive cervical cancer; LPD, lymphoproliferative diseases; lym, lymphoma; MALToma, MALT lymphoma; MFMS, multifocus multisystem; MFUS, multifocus unisystem; MPC, mesopharyngeal carcinoma; NPC, nasopharyngeal carcinoma; SCC, squamous cell carcinoma; UF, unifocus.

10. Infection and replication of EBV in macrophages

We demonstrated EBV infection and replication in macrophages in 1999 (84). In 2002, Masy *et al* showed that human monocytic cell lines transformed by EBV displayed EBNA-1 and LMP-1 but not EBNA-2, and these cells were tumorigenic after injection in nude mice (85). In 2004, Salek-Ardakani *et al* reported that EBV promoted human monocyte survival and maturation, and they mentioned that these cells may serve as a vehicle for the dissemination of the virus (86). Using experiments with tongue and buccal explants with EBV, Tugizov *et al* found that EBV first infected submucosal monocytes, then migrated into the epithelium and spread to oral epithelial cells. They also described EBV-positive macrophages in oral hairy leukoplakia tissues (87).

Using murine gammaherpesvirus 68, which is genetically related to EBV, Li *et al* showed that a replication-defective gammaherpesvirus 68 mutant virus established a long-term infection in macrophages, and the number of B cells harboring the viral genome was greatly reduced in the absence of lytic infection (88). On the other hand, an enhanced outgrowth of EBV-transformed chronic lymphocytic leukemia B cells was described to be mediated by coculturing with macrophage feeder cells (89).

11. Tumor-associated macrophages

Although the association with EBV was not examined, 85% of human macrophages expressed the Hodgkin's cell-associated antigen Ki-1 (CD30) *in vitro*, whereas normal human monocytes did not express the antigen (90). This finding indicates that the progression from monocyte to macrophage needs the expression of CD30 in at least 85% of the cases. EBV is suspected to participate in this progression with the production of IL-10. These findings will be evaluated in the 'Discussion' section.

The inflammatory process has been indicated to be a cofactor in carcinogenesis, where tumor-associated macrophages (TAMs) have been found to be a major component of the infiltrate of tumors (91). TAMs have also been described to enhance tumor progression and metastasis (92). Interactions between macrophages and lymphocytes in cancer have been discussed (93,94). Regarding RCC, 98 RCC patients were examined and correlations were identified for TAMs, microvessel density and the proliferative index with a tendency for poor prognosis (95) and the coculture of macrophages with RCC cells induced TAMs and the activation of signal transducers or activators (96). Macrophage recruitment was also suggested to be associated with the disease progression of Wilms' tumor (97).

We detected TAMs in many EBV-associated neoplasms including RCC, uterine carcinoma, oral cancer and others; TAMs, which were *in situ* hybridized with EBV antisense RNAs, were double-stained immunohistochemically with monoclonal anti-CD68 antibody (98). These findings indicate that TAMs infiltrate into EBV-associated neoplasms that express EBV transcripts, and they suggest a strong influence on oncogenesis.

12. Discussion

A summary of our experiments is shown in Table I. The sensitivity of the detection of EBV expression was higher with

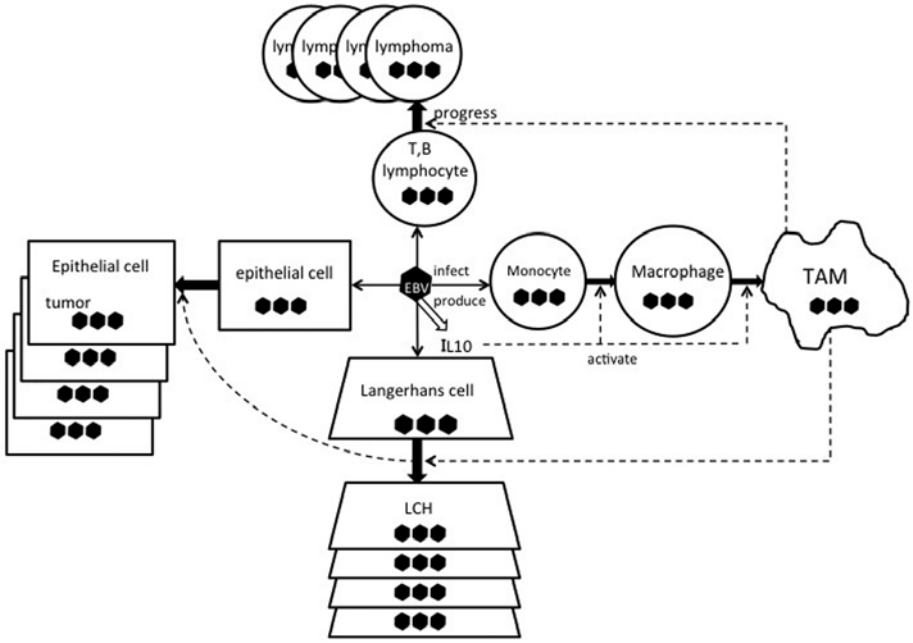

Figure 1. Expected pathways of oncogenesis of lymphocytes, Langerhans cells and epithelial cells with Epstein-Barr virus (EBV) as well as the expected pathways of activation of tumor-associated macrophages (TAMs) in the process of EBV oncogenesis. EBV infects and proliferates in T-lymphocytes, B-lymphocytes, Langerhans cells, epithelial cells and macrophages. In lymphocytes, Langerhans cells and epithelial cells, EBV-infected cells are transformed and grow tumors. In macrophages, IL-10, which is produced by EBV, activates monocytes and macrophages to grow TAMs resulting in the progression of EBV-associated tumors. Symbols in the figure: hexagon, Epstein-Barr virus; arrow, infection; white arrow, production; thick black arrow, progression; dotted arrow, activation.

the ISH method compared to immunofluorescence; *Bam*HIW mRNA ISH was the highest and the next was EBNA-LP mRNA ISH. Almost all human cancers examined showed EBV expression: not only EBNA2 but also EBNA LP, EBER1, LMP1 and *Bam*HIW. PCR was positive for all samples examined. These results indicate that many human neoplasms other than NPC and Burkitt's lymphoma correlate with EBV. The expression rate was almost uniform irrespective of the disease. This may be due to the limits of detection sensitivity and/or to the finding that all of the human organs examined were infected with EBV uniformly at the time of tumor development. Lung adenocarcinomas and SCCs (containing no case of lymphoepithelioma-like carcinoma) did not express EBV (data not shown); therefore, the hypothesis that EBV is associated with all human neoplasms is denied. In addition, the cell lines showed a higher incidence of positivity compared to the tissue sections, except for BZLF1 immunofluorescence.

Although the association between EBV and human neoplasms has been accepted in a restricted number of diseases, I propose that more attention should be paid to EBV-associated human cancers. The reasons are as follows. As indicated above, much epidemiological data have now been accumulated; in tissue cultures, EBV is one of the most potent transforming viruses (11); EBV persists in circulating memory cells and therefore will be found in all tissues (99); and in CTCL and LCH, some cases showed full clinical recovery after acyclovir treatment (37,73,75).

Moreover, *Bam*HIC coding rightward reading frame-1 (EBV BCRF1) protein shows 84% sequence homology to human IL-10 (100). IL-10 is a known growth and activation factor for B cells (101). EBV IL-10 could act on multiple cell types and inhibit cytokine synthesis by both T cells and NK cells (102). EBV-derived IL-10 is thought to play a role in the establishment of latent infection by suppression of the host immune system (103).

The macrophage involvement of EBV, which is described above, is also an important problem. IL-10 and viral IL-10 (v-IL-10) strongly reduce antigen-specific human T-cell proliferation by diminishing the antigen-presenting capacity of monocytes (104), and IL-10 promotes the differentiation of monocytes to mature macrophages and blocks their differentiation to dendritic cells (105). The transfection of v-IL-10 into murine cells resulted in tumors after 4 weeks and showed local immunosuppressive effects which depended on the v-IL-10 dose (106). The conservation and mutation of the v-IL-10 gene in various EBV isolates (107) and in human gastric carcinomas and NPCs were also reported (108). Although EBV association was not examined, Lee *et al* showed that bone morphogenic proteins (BMPs) in RCC promoted tumor proliferation through an IL-10-dependent M2 polarization of TAMs with mouse cell lines and 50 samples of human RCC, and they showed that BMP-6/IL-10/CD68 was associated with a poor prognosis (109). The interactions between EBV, IL-10, and TAMs are illustrated in Fig. 1.

Epidemiological information takes priority over the investigation of mechanisms, and the epidemiological evidence must be therefore accumulated. Virus-directed therapeutics against EBV-associated malignancies have been reported, which include EBV lytic phase induction followed by anti-herpesvirus drug mainly for EBV-positive lymphoid tumors (110), and for EBV-positive epithelial cell tumors (111), followed by radiation therapy for EBV-positive epithelial cell

tumors (112). Radiation therapy should be recommended for EBV-associated neoplasms, since EBNA2 is sensitive to ionizing radiation (81). It is suspected that infected Langerhans cells serve as a reservoir of EBV in oral epithelial cells (46), and following this infection, oral epithelial dysplasia and SCC are induced (28). The role of macrophages in the oncogenesis of EBV merits further study. The effect of acyclovir and radiation for treatment of EBV-associated neoplasms must be further studied.

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